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## STUDIES ON INTRADERMAL SENSITIZATION, II \*

### AN INTRADERMAL REACTION TO AGAR AND AN INTER- PRETATION OF INTRADERMAL REACTIONS

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#### AN INTRADERMAL REACTION TO AGAR

The author's studies on the reaction to agar, tho incomplete, are given discussion here because the observations thus far seem to afford a clue to the mechanism of intradermal reactions in general. The author undertook these experiments after a review of recent work on the physical theory of "anaphylatoxin"-formation. Certain aspects of these newer conceptions seemed to afford an explanation of the phenomena observed with emulsions of skin, as well as of the non-specific aspects of reactions to such substances as luetin, pallidin, and placentin. Of further interest was the recent announcement by Sherrick<sup>1</sup> that intradermally injected agar—among the best understood of the colloid antiferment-adsorbents, and, in 0.5% suspension, easily available for intradermal tests—gives rise to reactions on the administration of potassium iodid which are clinically indistinguishable from the luetin reaction and that an involuting luetin reaction can be revived by the same drug.

#### TECHNIC

The materials used in the first experiments in this direction were as follows: (1) A 0.5% agar suspension in physiologic salt solution (after being autoclaved, cooled, and shaken, this gel became a viscous translucent fluid which could easily pass through a fine needle); (2) a 20% suspension of bismuth subnitrate in salt solution; (3) a 20% suspension of bismuth subnitrate in olive oil; (4) olive oil alone.

All these materials were thoroughly sterilized in the autoclave before use. Instead of bismuth subnitrate, kaolin, another well-known antiferment-adsorbent, might have been used. The difficulty of introducing an insoluble powder into the cutis in salt suspension was so considerable and the violence of the reaction in the 1 successful attempt in 5 was such that the method was given up, and the oil suspension used to provide a so-called "foreign-body" reaction as a control comparison. Oil alone was used both as a control and to provide an illustration of the behavior of a neutral fat intradermally injected. The difficulty of injecting a powder suspension probably explains

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<sup>1</sup> Jour. Am. Med. Assn., 1915, 65, p. 404.

Sherrick's reported failure to secure a reaction from bismuth. The powder packs in the needle, and a small amount of salt solution can be filtered through, which raises a wheal but introduces very little bismuth.

#### EXPERIMENT 1

Intradermal injections were made in the left forearm (author's), after alcohol-ether sterilization, with 0.1 c.c. each of 0.5% agar, 20% bismuth subnitrate in olive oil, and of olive oil alone.

The oil alone produced practically no reaction, the slight areola disappearing in 36 hours. No papule formed.

Bismuth in oil, produced a marked reaction. On the 3rd day, a nodule had formed, the size of a marrow-fat pea. A factitial wheal could be produced on rubbing

4th, 5th, and 6th Days.—Itching especially mornings, with wheal-formation on rubbing. On one occasion a wheal formed increasing the diameter of the papule from 0.7 cm. to 1.7 cm.

8th Day and Thereafter.—This symptom disappeared, but the nodule has persisted with little sign of subsiding up to the present time (6 weeks). Nothing similar had been observed in previous reactions.

The agar produced a small discrete nodule, the size of a bird shot, with a rather large faint areola by the end of the 2nd day.

4th Day.—The nodule had flattened and all erythema had disappeared.

9th Day.—The nodule was reappearing with a translucent center and a marked areola.

11th Day.—A pea-sized papule with a soft, fluid-containing purplish center and a 3 cm. areola. The lesion then evacuated spontaneously, discharging a grumous bloody fluid. Immediate healing took place.

#### EXPERIMENT 2

A repetition of Experiment 1, on Mr. Kozilek. Oil alone and bismuth in oil gave the same results as before, except that no factitial wheal developed.

Agar produced an early reaction, marked, with deep induration, and a papule 8 mm. in diameter. Areola, 4 by 6 cm., transient.

9th Day.—Nodule persistent. Reaction began to light up spontaneously and develop a new areola.

10th Day.—Papule 8 mm. in diameter, hemispherical, with translucent, fluid-containing center. Areola 3.5 by 2.5 cm.

12th Day.—Nodule had increased to 1.5 cm. in diameter, was bluish-red in color, with a fluctuating center; areola 5 by 7 cm. Sensitive. Hemorrhagic character suggested by play of colors at margin.

13th Day.—Photographed (Fig. 1). Areola subsiding, but papule larger. Aspirated under asepsis. In spite of this the lesion continued to increase in size.

16th Day and Thereafter.—Lesion had reached a diameter of 2.5 cm., a raised, flattened, fluctuating, bulla-like lesion, purplish, with an infiltrated yellowish border. Free incision was made through a considerable thickness of skin, whereupon a grumous brownish fluid exuded. Lesion healed, leaving a small scar and a discolored patch. Absence of pain and lymphangitis rather striking.

Microscopically, the aspirated material was a mixture of pus and blood, and was sterile in smear and culture on a variety of media.

## EXPERIMENT 3

In order to see whether an active anaphylaxis to agar had been induced in the author by the 1st injection, a 2nd intradermal injection of an entirely fresh preparation of agar (0.5% in salt solution) was made in the other arm 22 days after the 1st injection and 11 days after the evacuation of the hemorrhagic lesion.

1st Day.—Prominent red nodule, 10 by 8 mm., firm, fairly sensitive, with an areola 4.5 by 6 cm.

3rd Day.—Areola gone; nodule same size as before, mildly erythematous and slightly sensitive. Site of the first injection negative.

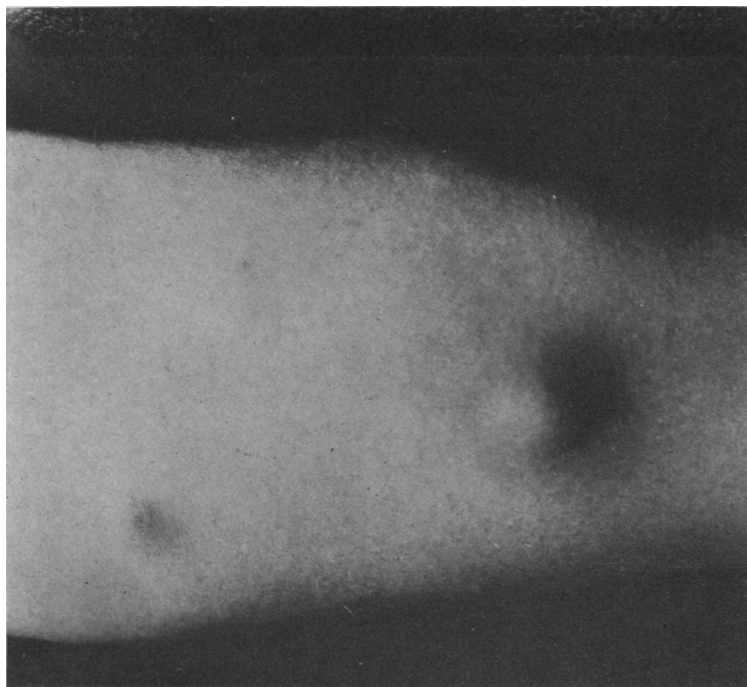


Fig. 1. Intradermal reaction to 0.5% agar on 13th day. The small papule to the right is a reaction to bismuth subnitrate in oil suspension, which is slowly involuting.

5th Day.—Nodule becoming purplish and soft, sensitive.

7th Day.—Nodule slowly enlarging. Contained fluid.

8th Day.—Papule high and prominent, a hemorrhagic fluid-containing lesion with a small faint areola. Distinctly sensitive and infiltrated. Site of the first injection, negative.

9th Day.—Nodule photographed. It ruptured spontaneously in the evening, discharging a bloody pus.

While the 1st reaction might be described as tardive, the 2nd passed through its cycle in about the average time for an ordinary luetin reaction. Otherwise, there was nothing to suggest an allergy towards agar after the 1st injection.

## RESULTS IN THE STUDY OF THE INTRADERMAL REACTION TO AGAR

Intradermal injection of 0.5% agar into 2 normal individuals who had not been taking potassium iodid, produced a papulo-pustular or hemorrhagic pustular reaction, the course of which in the cases observed was similar to familiar types of the reaction to luetin described in the literature.

The 1st reaction obtained in Experiment 1 corresponded closely with the torpid form of the reaction to luetin as described by Noguchi,<sup>2</sup> Jeanselme,<sup>3</sup> and others.

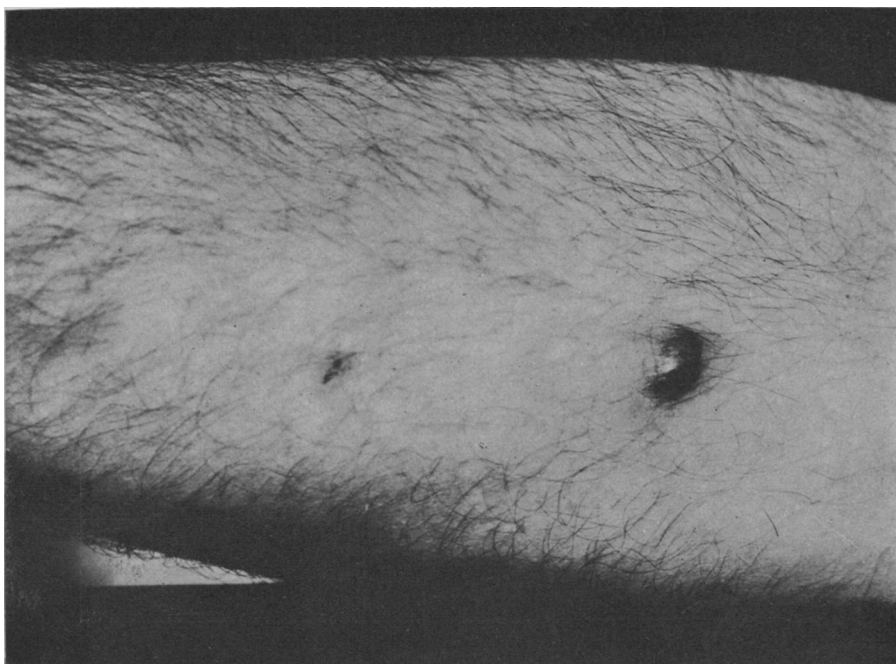


Fig. 2. Intradermal reaction to 0.5% agar, second reaction on 9th day. Hemorrhagic-pustular lesion just before rupture. The macule to the left is a recent scar.

The reaction obtained in Experiment 2 suggested a severe pustular reaction to luetin.

On 2nd injection of a fresh preparation of agar similar to the 1st, 22 days after the 1st injection, a 2nd typical papulo-pustular "luetin" reaction developed. Active anaphylaxis was not apparent either sys-

<sup>2</sup> Jour. Exper. Med., 1911, 14, p. 557.

<sup>3</sup> Bull. Soc. franc. de dermat. et de syph., 1914, 25, p. 27.

temically or at the site of previous injection. The only difference between the two reactions was in the somewhat more rapid course of the 2nd.

The final stage of the reaction as observed thus far, is perhaps more distinctly hemorrhagic than the ordinary reaction to luetin.

Intradermal injection of a neutral fat produced no significant response.

The reaction to an insoluble non-protein powder (bismuth subnitrate) suspended in oil, after passing through an active early stage with nodule- and wheal-formation, subsided after about 10 days to an indolent nodule, representing probably an irritation phenomenon. The lack of a definite cycle such as is found in the agar and skin reactions may be due to the difficulty experienced by the tissues in disposing of the substance. The earlier phenomena seem to require, for their explanation, more than the conception of a merely mechanical process of local injury.

#### DISCUSSION OF THE RESULTS

The interpretation of these results and the discussion of intradermal reactions such as those to luetin, pallidin, placental extracts, etc., here offered, are based on recently developed views of the physical mechanism of anaphylaxis, as outlined in the work of Besredka and Ströbel,<sup>4</sup> Bordet,<sup>5</sup> Ritz and Sachs,<sup>6</sup> Keysser and Wassermann,<sup>7</sup> Kopaczewski and Mutermilch,<sup>8</sup> Doerr,<sup>9</sup> Bordet and Zunz,<sup>10</sup> Fenyvessy and Freund,<sup>11</sup> Dold and collaborators,<sup>12</sup> Jobling and his co-workers,<sup>13</sup> and various protagonists of the humoral view represented by Friedberger and his collaborators.<sup>14</sup> Especially serviceable are the discussions by Doerr<sup>9</sup> (he covers the entire field) and the summaries of the literature in the articles by Jobling and his co-workers.

In recent years two rival conceptions of the mechanism of anaphylactic intoxication have been conspicuous. That espoused, notably, by Friedberger and his school,<sup>14</sup> maintained, in substance, that the fate

<sup>4</sup> Compt. rend. Soc. de biol., 1911, 71, p. 413.

<sup>5</sup> Ibid., 1913, 74, p. 225.

<sup>6</sup> Berl. klin. Wchnschr., 1911, 48, p. 987.

<sup>7</sup> Ztschr. f. Hyg. u. Infektionskrankh., 1911, 68, p. 535.

<sup>8</sup> Ztschr. f. Immunitätsf., 1914, 22, p. 539.

<sup>9</sup> Wien. klin. Wchnschr., 1912, 25, p. 331. Kolle and Wassermann, Handb. d. pathogenen Microorganismen, 1913, 2, p. 947.

<sup>10</sup> Ztschr. f. Immunitätsf., 1914, 22, p. 42; p. 49.

<sup>11</sup> Ibid., p. 59.

<sup>12</sup> Ztschr. f. Immunitätsf., 1912, 15, p. 171; 16, p. 475; 1913, 18, p. 207. Berl. klin. Wchnschr., 1912, 49, p. 2310.

<sup>13</sup> Jour. Exper. Med., (a) 1915, 21, p. 239; (b) 1914, 20, p. 37. (c) Arch. Int. Med., 1915, 15, p. 286.

<sup>14</sup> Ztschr. f. Immunitätsf., (a) 1913-14, 20, p. 405; (b) 1913, 17, p. 506; (c) 1912, 12, p. 241.

of foreign proteins introduced into the body parenterally is accomplished through the proteolytic activity of specific enzymes which in an antigen-amboceptor reaction liberate from the digested protein matrix (antigen), the toxic substances responsible for the symptoms. This view, substantially unmodified, is the one most familiarly applied in the interpretation of the clinical phenomenon of anaphylaxis as ordinarily conceived. Within the past 5 years, however, the work of Besredka and Ströbel,<sup>4</sup> Bordet,<sup>5, 10</sup> Ritz and Sachs,<sup>6</sup> Keysser and Wassermann,<sup>7</sup> Doerr,<sup>9</sup> Mutermilch and Kopaczewski,<sup>8</sup> and numerous other investigators, has compelled considerable modification of the older conceptions. Besredka and Ströbel, and Bordet, by showing that the exposure of normal guinea-pig serum to the action of 0.5% agar *in vitro* caused it to assume toxic properties which were apparent on re-injection into the same animals, opened the way for the conception that the matrix of "anaphylatoxin" lies, not in the parenterally injected substance, but in the serum or cells of the injected animal. The objection of the Friedberger school that the toxic effect of agar-treated serum was due to the effect of the serum enzymes on the protein of the agar itself was recently met by Bordet and Zunz,<sup>10</sup> who showed that an efficient "anaphylatoxin" could be produced by the action of pararabine, a practically nitrogen-free agar derivative. The same effect was demonstrated for a non-nitrogenous colloid—sodium pectin—by Kopaczewski and Mutermilch.<sup>8</sup> Numerous other investigations in the meanwhile had shown that a variety of substances, such as coagulated albumins, killed bacteria, certain toxins, and even such inert substances as kaolin, fuller's earth, and barium sulfate are capable of initiating the formation of "anaphylatoxin" from guinea-pig serum *in vitro*.

The mechanism of the action of these substances has been a matter of controversy. As a result of the investigation of bacterial "anaphylatoxin," Friedberger<sup>14</sup> was led to modify his theory to provide that the antigen-amboceptor reaction preceded the formation of "anaphylatoxin" and was the specific part of the reaction, the "anaphylatoxin" produced being the same regardless of the antigen. Subsequent investigations further tended to show that both specific antigen and amboceptor were unnecessary (Doerr,<sup>9</sup> Jobling<sup>13</sup>). Certain investigators committed themselves rather definitely to an exclusively physical theory of colloid interaction (Doerr<sup>9</sup>). Other investigations have tended to substantiate the view, apparently, that the development of "anaphylatoxin" in serum, for example, occurs as a result of lytic ferments normally pres-

ent, but inhibited by the presence of antiferment.\* Agar, starch, kaolin, etc., act by adsorbing the antiferment, thus inhibiting its action, and liberating or uncovering the ferment proper. It is the uncovered ferments which then split the serum proteins up into toxic products responsible for the symptoms. In other words, the matrix of the toxin is now thought to be, not in the parenterally introduced substance, but in the serum or other proteins of the animal. The recent work of Jobling<sup>13b</sup> and his associates has been interpreted as showing that the antitrypsin (antiferment) is an unsaturated lipoid and that its action may be inhibited not only by adsorbents such as agar but by saturation with iodine, for example. These authors claim clinical application for this view in the well-known action of iodids in promoting lysis of granulomatous tissue. The specificity of the Abderhalden reaction has also been attacked on experimental, as well as clinical, grounds (Jobling, Eggstein, and Petersen<sup>13a</sup>). Agar, starch, etc., when used as substrates, give positive reactions with guinea-pig serum (Plaut<sup>15</sup>). Peiper<sup>16</sup> and Friedemann and Schoenfeld<sup>17</sup> regularly obtained positive Abderhalden reactions by adding starch to serum. Jobling and his collaborators<sup>13a</sup> showed that the placental tissue used in the reaction was not digested, but became more resistant to the action of trypsin, as a result presumably of adsorption of antitrypsin. These authors conclude "that the (serum) proteases are not specific, the placental tissue being found most efficacious possibly because of purely mechanical factors (surface exposure), as is indicated by the wide range of clinical conditions in which the placental substrate gives positive results." The placental tissue, then, acts as an antiferment-adsorbent, and not as the antigen on which a specific ferment in the serum acts. The matrix, therefore, of the protein split products which give a positive reaction is in the serum and not the substrate, according to this view.

The application of the physical theory of anaphylaxis, as distinguished from the humoral or chemical view, to the mechanism of intradermal reactions, develops a number of interesting and suggestive pos-

\* Whether the effect of an anaphylatoxin-forming agent, such as agar, kaolin, etc., is accomplished through proteolysis by ferments or through changes in colloid equilibrium in the affected tissues, serum, etc., need not impair the validity of the arguments advanced in this study against specificity and in favor of a common non-specific mechanism for the reactions subsequently discussed. The essence of the author's contention is that the intradermal reactions considered are not specific antigen-antibody reactions. The details of the non-specific mechanism, on the other hand, must be considered as unsettled. The conception of the mechanism has been phrased here in terms of the ferment proteolysis of a non-specific matrix because this view is, for the time being, supported by accessible experimental investigations.

<sup>15</sup> München. med. Wchnschr., 1914, 61, p. 238.

<sup>16</sup> Deutsch. med. Wchnschr., 1914, 40, p. 1467.

<sup>17</sup> Berl. klin. Wchnschr., 1914, 51, p. 348.



sibilities, especially when it is used to account for discrepancies and inconsistencies in what were at first accepted as specific tests in the older sense—that is, tests for specific amboceptors by the injection of specific antigens. Altho it would not be justifiable in the present status of experimental knowledge to apply the physical theory to the exclusion of the chemical, and to deny flatly the participation of antigen, amboceptor, and complement in the reaction, the physical theory seems unusually well fitted to harmonize and explain a confusion which has not tended to diminish with increased clinical experience under the older conceptions.

#### THE REACTION TO AGAR

The reactions to the intradermal injection of agar, as described in the first part of this report, seem to be the simplest and most convenient starting point for the application of the physical theory, in view of the prominent place that agar has held in the experimental work on which this theory is grounded. To recall the basic facts, agar was among the first of the colloidal producers of anaphylatoxin to be recognized, attention having been called to its properties by Besredka and Ströbel<sup>4</sup> and Bordet.<sup>5</sup> Working with a colloidal gel of 0.5% agar in physiologic salt solution, Bordet showed that a 3-hour exposure to its action at 37 C. would render a previously non-toxic guinea-pig serum extremely toxic for guinea-pigs, the symptoms induced being those of anaphylactic shock. The contention that this effect was due to adsorption was criticized by Friedberger<sup>14</sup> on the ground that agar contained enough protein (11%, König) to account for its behavior on the score that it acted as a protein antigen. This contention seems finally to have been met by the work of Bordet and Zunz<sup>10</sup> with pararabine (nitrogen-free agar) and by the work of Mutermilch and Kopaczewski<sup>8</sup> on pectin, Keysser and Wassermann<sup>7</sup> on kaolin, Nathan<sup>18</sup> on starch, and similar studies. The behavior of agar in an Abderhalden test with guinea-pig serum,<sup>15</sup> which normally contains large amounts of protease, has further tended to establish its action as that of an antiferment-adsorbent, and to place it in the same group as kaolin, and the other inert agents which in anaphylatoxin-formation must play a physical rather than a chemical rôle.

The transference of in-vitro results in the case of such adsorbents to in-vivo conditions, is only in its beginning. In the case of small laboratory animals, with serum of high protease content, the results should

<sup>18</sup> Ztschr. f. Immunitätsf., 1913, 18, p. 636.

be more clear-cut than in man. There would seem to be no reason *a priori*, however, why such a physical property as adsorptive capacity should be suspended on the parenteral introduction of a substance into the blood, or even into a local focus in the skin. Friedberger and Tsuneoka<sup>14b</sup> have recently studied the effect of kaolin *in vivo* (intravenous injection). Coming from the opposing camp, Friedberger's admission in this connection seems highly significant—"the toxicity of kaolin is not to be explained as of mechanical origin. It depends rather on adsorption *in vivo* of certain substances from cells, essential to the life of the organism."

To construct, then, a scheme for the action of intradermally injected agar in accordance with the theory of its action as a physical process, it may be conceived possible that the part which it performs is simply that of withdrawing from either the blood serum or the lymph, or from the tissues into which it was injected, or from all these, the ferments which protect them from autolysis. Autolysis then occurring, anaphylatoxins would be formed in a focal necrosis as the starting point of a reaction.

The matrix of this anaphylatoxin seems more open to dispute than the idea of its formation. Blood serum, leukocytes, and the cutaneous tissues themselves may serve as matrices. Human serum, for example, does not contain the relatively large amounts of protease found in the laboratory animals, the proteases in man being largely in the leukocytes (Jobling). It is possible, however, that adsorption of antiferment at a given point causes a rise in protease content in human serum such as occurs in tuberculosis, carcinomatosis, and pregnancy. The fall in antitryptic titer of serum in patients whose antitrypsin is being inhibited by iodids (Jobling and Petersen<sup>13c</sup>), is in line with such a view to some extent. Even more applicable is the observation of Börnstein, Nast, and Nickau,<sup>19</sup> discussed later, that a non-specific lytic action is developed in the blood after luetin injections. Favoring the significance of the surrounding tissues in the reaction, is the much more definite picture obtained by intradermal injection as compared with subcutaneous injection in all the types of reactions considered in this report.

Fixation of the adsorbing agent at the site of injection has seemed to the author an essential feature of the mechanism, necessary to explain the focal character. The slow diffusion of many substances from points of intradermal injection is a common observation, and was especially apparent in the injections of washed blood clot, for example, in which

<sup>19</sup> Arch. f. Dermat. u. Syph., 1914, 120, p. 240.

the zone of reaction corresponded exactly to the discoloration from blood pigments. It is possible that this slower diffusion accounts for the more striking reaction to intradermal injection as compared with that to subcutaneous injection,—instead of an active participation of the dermal cells as matrix for the anaphylatoxin. In studies of insect bites<sup>20</sup> that show a slow development (black fly), the author has felt that a local fixation of the toxic agent was essential to the explanation of the clinical and pathologic mechanism of the reaction. Such a fixation would of course reach an extreme in the case of an insoluble substance, such as bismuth subnitrate or kaolin, and might be a factor in the violence of the early reaction. It is conceivable that the action of certain supposedly inert “foreign bodies” may, in its earlier stages, be due to a physical adsorbent effect heightened by the mechanical effectiveness of their fixation.

The time element in a reaction, while to some extent a function of the degree of fixation of the injected adsorbent, may be conceived as depending also on the active resistance offered by the living cells to the action of the liberated proteases. This resistance, whether on the part of tissue or blood cells (leukocytes), would take the form perhaps of a formation of an anti-enzyme to replace that adsorbed, as well as of a possible mechanical removal of the adsorbent by phagocytosis. If the resistance overbalances the action of the adsorbent, involution takes place. If on the other hand, proteases were liberated with special ease or in special abundance, or the adsorption were very efficient, as might be the case under pathologic conditions, focal necrosis and autolysis would get the upper hand and the reaction would progress to pustule- or abscess-formation with evacuation of adsorbent and products of the digestion. Finally, in the event of a balance of this sort being reached, it is conceivable that it might be disturbed by another injection in the immediate vicinity, or the introduction of another antiferment-inhibiting agent such as iodine through the blood. This might, as mentioned later, provide a rationale for Sherrick's observations on the lighting up of agar and starch injection sites on the administration of iodids.

The clinical course of the agar reaction strongly suggests the plausibility of such conceptions of its mechanism. The true papular reaction developing within from 24 to 48 hours after injection represents supposedly the active fight of the surrounding tissues, and perhaps leukocytes, to produce anti-enzymes to replace those adsorbed. This phase

<sup>20</sup> Jour. Cutan. Dis., 1914, 32, pp. 751, 830.

occupies several days, and is accompanied by all the signs of acute inflammation. At the center of the lesion, where the concentration of the adsorbent is highest and the formation of anaphylatoxin by the liberated proteases most active, necrosis occurs, accompanied by proteolysis. This proteolysis is a conspicuous feature of the reactions to agar thus far seen by the author, in their later stages. The rapidity with which in one case, for example, the subcutaneous tissues were literally dissolved into a sterile grumous hemorrhagic fluid, was highly suggestive of a powerful lytic ferment action. This autolysis was conspicuous after the inflammatory symptoms representing the defensive reaction of the tissues had largely subsided.

Reactions in which constitutional symptoms occur in conjunction with the local ones, while not thus far observed with agar, may be conceived as following the escape of locally formed anaphylatoxin from the reaction site into the blood, or as resulting from the lysis of serum proteins by proteases temporarily uncovered by the adsorption of a considerable amount of serum antiferment at the site of injection of the adsorbing agent. If it be correct to place the leukocytes first as antiferment-carriers in the human body, for example, their function in the leukocytic wall that surrounds such local foci is apparent. Their antiferments guard the body against a general uncovering of its own proteases, serving also to restore the balance destroyed by the local effect of an antiferment adsorbent.

Adsorption reactions of the type which that to agar represents in the scheme outlined here, are obviously non-specific. The body does not according to this view, react to agar as such, but to adsorption of antiferments. The symptoms, then, are not evidence of the specificity of the injected substance in an antigen-antibody reaction, but merely the result of allowing the body to digest its own proteins by adsorbing or inhibiting its antiferments. The only value of such reactions, therefore, from the clinical standpoint, would be to measure the enzyme balance or lability, and the amount and intensity of action of non-specific proteases in the body. The establishment by this method of the existence of ferment instability, etc., in a given case may prove to have clinical diagnostic value, and afford invaluable information on the *modus operandi* of pathologic agents.

It may be argued that the agar reactions observed, represent a special case, and that they would not occur in persons who had not already subjected themselves to a series of intradermal injections such as those of skin emulsion, bismuth, and the like. The question of the

amount of variability possible in the reaction of normal skin, aside, it is scarcely to be expected that a reaction to agar will occur in all individuals, nor is it necessary that it should. If the reaction to agar is an expression of ferment balance or ferment activity in the serum or tissues, it will undergo wide variations in normal and pathologic conditions. It would, in fact, be an additional piece of evidence in favor of the wide applicability of the physical theory, to be able to show that normal individuals who do not ordinarily react, could prepare themselves for reaction to a non-specific substance such as agar by a series of tests on themselves with normal-skin emulsion. That the agents which cause reaction to skin emulsions, to palladin, to placental extracts, to luetin, etc., can likewise cause a non-specific but clinically similar reaction to an antiferment adsorbent would almost amount to a demonstration of the essential identity of the mechanisms and the consequent non-specificity of the clinical tests mentioned. The settlement of all these questions must of course await further study of the agar reaction, in normal and pathologic individuals.

#### THE MECHANISM OF THE LUETIN REACTION

While the luetin reaction seems several steps removed from the plainer case of the agar reaction, a close examination of experimental evidence bearing on it, gives ground for placing it, in large part at least, in the class of antiferment-adsorbent or anaphylatoxin reactions, and treating it as in the case of the reaction to agar, not as specific for syphilis, but as a measure, albeit perhaps a sensitive one, of the ferment-antiferment balance, and of the amount or intensity of action of non-specific proteases in the body of the syphilitic.

Of immediate interest in this connection is the recent report by Börnstein, Nast and Nickau,<sup>19</sup> previously mentioned, of a non-specific lytic reaction in the serum of certain syphilitics. This reaction was observed to develop after intradermal injections of luetin. In so far as such findings indicate a relation between non-specific ferment activity and the luetin reaction, they have direct application to the previous contentions. The parenteral injection of an antiferment-adsorbent, by lowering the antiferment content, would uncover serum proteases of a non-specific character, and this could explain the reaction observed by these authors. This effect has been observed by Jobling and Petersen<sup>13c</sup> in the inhibition of antitrypsin by iodine, as mentioned. They report, it will be recalled, the demonstration *in vivo* in the case of syphilitics receiving potassium iodide, of a definite lowering of anti-

tryptic activity in the blood. This should mean non-specific protease in small amounts in the blood. If luetin is an antiferment-inhibitor, it could conceivably uncover enough protease to account for the reaction observed by Börnstein, Nast and Nickau.<sup>19</sup>

Argument of this indirect type is supported by an examination of luetin itself from the standpoint of the physical conception of anaphylatoxin-formation. Noguchi's<sup>2</sup> original description of the preparation and ingredients is in substance as follows. *Spirochaeta pallida* from ascitic-agar cultures are mixed with those from ascitic-fluid cultures, the agar mass in the first case, filled with the organisms, being ground in a sterile mortar, and the fluid culture added. Luetin, therefore, when ready for use, contains agar, diluted with ascitic fluid to an undetermined degree, and the fragmented bodies of spirochetes. The further dilution with salt solution is made at the time of injection. A control suspension consists of the similarly prepared culture media, uninoculated.

In the light of this description, the following considerations present themselves: Both the control and the luetin proper contain at the outset one of the best-known antiferment adsorbents—agar. Luetin, in contradistinction from the control, contains in addition the fragmented bodies of *Spirochaeta pallida*.

The production of so-called bacterial anaphylatoxin, probably by a mechanism of adsorption (Doerr<sup>9</sup>), has been demonstrated for a variety of organisms, including forms as closely related to the *Spirochaeta pallida* as the spirochetes of chicken spirillosis and of Russian relapsing fever (Mutermilch, Dold and Aoki, quoted by Doerr). In 1913, Nakano,<sup>21</sup> working with pure cultures, reported the formation of bacterial anaphylatoxin from guinea-pig serum by *Spirochaeta pallida* in vitro. On the basis of this experimental evidence, it seems not unreasonable to suggest that the fragmented *Spirochaeta pallida* in luetin may be capable of anaphylatoxin-formation in vivo on intradermal injection, the effect to be added to that produced by the agar anaphylatoxin provided for by the presence of that substance in the preparation.

These considerations provide at once a not unacceptable physical explanation of the greater efficiency of luetin as compared with its control. Luetin contains two adsorbents instead of one. The presence of an active antitrypsin-adsorbent in the control (agar), moreover,

<sup>21</sup> Arch. f. Dermat. u. Syph., 1913, 116, p. 281.

explains such results as those of Boas and Ditlevsen,<sup>22</sup> who in a series of cases, using an authentic preparation, obtained in lues tertius and lues hereditaria nearly as many reactions of almost the same intensity from the control preparation as from the luetin itself. Other non-specific or doubtful results have been reported by Burnier,<sup>23</sup> Cederkreutz,<sup>24</sup> Kaliski,<sup>25</sup> Schmitter,<sup>26</sup> Jeanselme,<sup>3</sup> Joltrain,<sup>27</sup> Bruck,<sup>28</sup> and Baermann and Heinemann.<sup>29</sup> Jeanselme, for example, obtained largely torpid positives. The problem of securing a luetin which will cause a reaction in a syphilitic skin and not in a normal one, may be one of securing such a dilution or proportion in the ingredients as will serve as a measure of the ferment hyperactivity or lability rather than one of providing specific antigen for a specific amboceptor to react with. The obvious difficulty in striking such a mean without accurate knowledge of the amount of each ingredient necessary to produce a local anaphylatoxin reaction, is apparent, and may well explain the erratic behavior of certain specimens of luetin, attested by workers. Moreover, the tendency to discard the control after a few injections, observed in several favorable reports, has perhaps prevented some of these considerations from standing out as clearly as they might.

Clinical resemblance between the agar reactions observed and the luetin reaction, has impressed the author, even in an experience with the former which is much too incomplete to establish the foregoing considerations. In the reactions seen thus far, the conventional type of marked luetin reaction and the tardive form, as judged by the criteria of Noguchi,<sup>2</sup> Benedek,<sup>30</sup> Jeanselme,<sup>3</sup> Boas<sup>22</sup> and others, have been simulated to a degree which, allowing for the difference in the concentration, etc., of the adsorbents, is highly suggestive. Such close resemblance argues somewhat of a common mechanism.

Mention should be made at this point of Sherrick's<sup>1</sup> observation that reactions to intradermally injected agar light up on ingestion of potassium iodid.

In his preliminary report, thus far the only account he has published, he mentions moderate transient reactions from intradermally injected agar, following doses of 0.07 c.c. of a "less than 1%" solution. He lays special stress on

<sup>22</sup> Arch. f. Dermat. u. Syph., 1913, 116, p. 852.

<sup>23</sup> Bull. Soc. franc. de dermat. et de syph., 1914, 25, p. 31.

<sup>24</sup> Finske läk.-sällsk., handl., Helsingfors, 1913, 1, p. 407.

<sup>25</sup> N. Y. Med. Jour., 1913, 98, p. 24.

<sup>26</sup> Jour. Cutan. Dis., 1913, 31, p. 549.

<sup>27</sup> Bull. Soc. franc. de dermat. et de syph., 1913, 24, p. 507.

<sup>28</sup> Versamml. deutsch. Naturforsch. u. Aertze in Wien, 1913.

<sup>29</sup> München. med. Wchnschr., 1913, 60, p. 1537.

<sup>30</sup> Ibid., p. 2033.

the lighting up of the reaction following the administration of potassium iodid, and it is conceivable that, using this drug, he obscured the outcome of what might have been reactions to agar in certain cases, resembling those in the author. His dosage, moreover, was distinctly lower than the author's.

The lighting up of both luetin and agar intradermal-injection sites on the administration of potassium iodid, as reported by the same author, is an interesting additional evidence of the essential similarity of the two reactions as to mechanism, and a further means of linking intradermal reactions with other ferment reactions elsewhere in the body. Jobling and Petersen<sup>13c</sup> in their work on iodine action on antitrypsin, already mentioned, quote Michaud and Wells and Hedonberg as having demonstrated an increased concentration of iodine in necrotic tissues, especially when softening is in process. The function of this iodine is supposed by Jobling and Petersen, to be that of an inhibitor of antitrypsin, an action which they have demonstrated on serum. The administration of iodids supposedly supplies iodine to inhibit antiferment action in a focal necrosis and autolysis ensues. The sites of the injection of agar and luetin are presumably focal necroses. If they are conceived as due to the action of ferment-inhibitors, the involution possibly represents the reaching of a local balance between increased amounts of protease and antiferment. As soon as another antiferment-inhibitor (iodine from potassium iodid) appears on the scene, the balance is disturbed and the reaction sites light up, perhaps more violently than before. The 1st antiferment-adsorber came from without (agar or luetin); the 2nd came by way of the blood (iodine). That there is no essential difference between the action of the 1st and the 2nd seems plausible, and the clinical resemblance between the reaction to iodid and the reactions to luetin and agar is rather to be expected than otherwise.

Without wishing to overrate somewhat circumstantial evidence, the author believes that a stronger case than ever before can be made for non-specificity in the strict sense, in the luetin reaction. It seems reasonably open to interpretation as, at least in part, a local adsorption phenomenon, due to anaphylatoxin liberated by uncovered proteolytic ferments from a non-specific matrix in the tissues or the serum of the syphilitic, and not in the injected spirochetes. Its legitimate function may be conceived as that of a measure of ferment activity or the lability of ferment-antiferment balance.

#### REACTIONS BASED ON PROTEIN AND PROTEIN-BACTERIAL EXTRACTS

The problem of accounting for intradermal reactions increases distinctly in complexity with the consideration of organ extracts and tissue suspensions, with or without a content of bacteria.

The work of a number of investigators (Dold<sup>12</sup> and others), has established the toxicity of organ extracts, even for homologous animals. The observations cover a wide range of tissues and various methods of preparation, including tissue juices—as from placenta—and cellular and filtered extracts in various menstrua, etc. A recent investigation by Schenk<sup>21</sup> ascribes the toxicity of placental juices to the presence of fibrin ferment.

<sup>21</sup> Ztschr. f. Immunitätsf., 1914, 22, p. 229.



While it is impossible to enter into an extended discussion of these toxic properties, the possibility of their influence on intradermal injections must be borne in mind. However, in the rapidly increasing variety of anaphylatoxin-forming substances the action of which is being ascribed to physical rather than to chemical phenomena, are included precipitated and coagulated proteins of many kinds, such as boiled antigen, boiled horse serum (Friedberger and Castelli, quoted by Doerr<sup>32</sup>), boiled precipitates (Friedberger and Jerusalem cited by Doerr), in which the action of contained enzymes is ruled out, as well as such combinations as inactivated horse serum and guinea-pig serum (Friedberger<sup>34</sup> and Nathan<sup>35</sup>). The adsorptive power of placental tissue has been particularly discussed by Jobling, Eggstein and Petersen<sup>36a</sup> in connection with the Abderhalden reaction mentioned.

The contention is therefore fairly well grounded, that protein suspensions may act as ferment-adsorbents and give rise to anaphylatoxins by a physical mechanism of the type heretofore considered.

#### THE REACTIONS TO PALLIDIN AND SYPHILIN

The attempt to secure a cutaneous test for syphilis by the use of spirochete-containing organ extracts preceded, by some years, Noguchi's luetin. Liver-tissue extracts, in particular, formed the basis of such preparations as "syphilin," employed by Nicholas, Favre, Gautier and Charlet,<sup>32,33</sup> Fontana<sup>34</sup> and others, with somewhat inconstant results, approaching those later more clearly demonstrated by luetin and pallidin. "Pallidin" as employed by Klausner,<sup>35</sup> after Fischer,<sup>36</sup> is a suspension of lung tissue from pneumonia alba, rich in *Spirochaeta pallida*; heated to 60 C. before use.

Of interest in this connection is Nakano's<sup>21</sup> observation that extracts of syphilitic liver will produce anaphylatoxin in vitro with syphilitic serum, but not with normal serum. The production of anaphylatoxin becomes more marked the older the lues from which the serum is taken. Addition of guinea-pig complement markedly increases the anaphylatoxic effect of the serum.

It is possible that the action here observed is not a simple one, and at first glance an antigen-amboceptor reaction is certainly suggested by the failure of Nakano's controls of normal-liver extract and syphilitic serum to react. It should not be forgotten, however, that spirochete-containing liver extract can behave as spirochetes would, and that the anaphylatoxin developed may be due to them. The failure of

<sup>32</sup> Compt. rend. Soc. de biol., 1910, 68, p. 257.

<sup>33</sup> Lyon médical, 1910, 114, p. 621.

<sup>34</sup> Dermat. Wehnschr., 1912, 54, p. 109.

<sup>35</sup> Arch. f. Dermat. u. Syph., 1914, 120, p. 444.

<sup>36</sup> Wien. klin. Wehnschr., 1913, 26, p. 49.

the extract of syphilitic liver to develop anaphylatoxin in contact with normal human serum can be accounted for by the relatively little protease (Jobling, Eggstein, and Petersen<sup>13</sup>) in normal human serum. However, variation in the protease and antitrypsin content of human serum has been demonstrated in several pathologic conditions, notably carcinoma, tuberculosis (Jobling), pregnancy, and pneumonia. To quote these authors, "it seems probable that in various pathological conditions proteases normally confined to the leucocytes in the human being appear in the blood, where their presence can be demonstrated by a method which removes the antiferment without injuring the ferment." Such a view applied to syphilis would provide an acceptable explanation for Nakano's observation that anaphylatoxin was generated only in contact with the pathologic (syphilitic) serum, which supposedly contains more protease than the normal. Nakano's<sup>21</sup> own observation that the effect was greatly heightened by the addition of a serum rich in protease (guinea-pig complement) is confirmatory of this view.

In such a reaction, then, the spirochetes conceivably act as adsorbents, liberating or uncovering the increased protease in syphilitic serum. Such protease need not be specific any more than in the case of pregnancy, carcinomatosis, tuberculosis, or pneumonia. That addition of a distinctly non-specific protease such as that of guinea-pig serum accelerates the reaction seems further to weaken the contention that the reaction is a specific one.

It seems reasonable to suppose, then, that the local reaction to syphilitic-tissue extract is to some extent the result of antiferment-adsorption by the contained spirochetes. The proteolysis which produces the anaphylatoxin is made possible by the uncovering of non-specific proteases in syphilitic blood as part of the pathologic picture of the disease. The observations of Börnstein, Nast and Nickau<sup>19</sup> relative to non-specific lytic effects from the serum of syphilitics will be recalled as directly in accord with this view.

On a similar basis the behavior of "pallidin" (Klausner<sup>35</sup>) can be accounted for, with the application of special factors in special cases. "Pallidin" as described by Klausner, who used Fischer's method of preparation, is a suspension of lung tissue and spirochetes in physiologic salt solution (0.5% phenol), heated to 60 C. Jobling, Eggstein and Petersen,<sup>13a</sup> in discussing the behavior of placenta in the Abderhalden reaction, mention lung tissue as second to placental tissue in efficiency, as a substrate. If this parallelism between the behavior of placental and lung tissue extends to the adsorbent properties experimentally

determined by these authors for placenta, an index to its effect in "pallidin" is obtained. The superiority claimed for "pallidin" over other spirochete-containing tissue extracts may therefore be that of a more efficient adsorbing base as well as a rich spirochetal content.

Boas and Stürüp<sup>37</sup> have followed up Klausner's results on pallidin, and in addition have shown that "pallidin" reactions can be produced in late syphilis by the use of extracts of chancroidal bubo taken from non-syphilitics. This observation can also be reconciled to the views here presented by recalling that such a suspension is again, a mixture of coagulated protein plus bacteria (*Ducrey strepto-bacillus*) and that there is reasonable ground for expecting it to have anti-ferment-adsorptive properties, even tho they have not as yet been demonstrated as such. The local anaphylatoxin reaction produced by such a preparation also rests on the well-supported presumption of the presence of increased amounts of non-specific proteases in the serum or tissues in late syphilis.

The reported production of luetin reactions by Boas and Ditlevsen<sup>22</sup> with gonococcal and colon-bacillus suspensions in late syphilis without complicating gonorrhea or gastro-intestinal symptoms, represents the non-specific anaphylatoxin reaction from bacteria minus the tissue-protein-suspension adsorbent. The author's own apparent production of a luetin reaction in a late syphilitic by an emulsion of normal skin represents at the other extreme, anti-ferment-adsorption and local anaphylatoxin-formation by tissue protein minus the bacterial adsorbent.

#### INTRADERMAL TESTS FOR PREGNANCY

In the effort to apply the theoretical mechanism of the Abderhalden reaction as elaborated by its discoverer, to clinical conditions, several observers have undertaken intradermal tests with various extracts and fractions of placental tissue. The favorable results as to specificity reported by Engelhorn and Wintz<sup>38</sup> have not been corroborated by other observers, notably Esch,<sup>39</sup> De Jong,<sup>40</sup> and Falls and Bartlett.<sup>41</sup> De Jong, using ground placenta with ground-muscle tissue as control, found the reaction worthless in cattle. Falls and Bartlett, using whole placenta and various fractions in cutaneous, subcutaneous, and intradermal tests could find no evidence of specificity. They conclude that the pregnant woman is certainly not a sensitized woman in the usual sense.

<sup>37</sup> Arch. f. Dermat. u. Syph., 1914, 120, p. 730.

<sup>38</sup> München. med. Wehnschr., 1914, 61, p. 689.

<sup>39</sup> Ibid., p. 1115.

<sup>40</sup> Ibid., p. 1502.

<sup>41</sup> Chicago Path. Soc., 1915, 9, p. 249.

In the interpretation of this evidence for non-specificity Jobling, Eggstein, and Petersen's<sup>13a</sup> experimental studies of the marked antiferment-adsorptive capacity of placenta again apply. Taken in conjunction with the known rise in antitryptic titer in the serum of pregnant women, which implies a rise in proteases, the mechanism so often brought forward in this paper is provided for. It may be applied to this intradermal reaction precisely as in the case of the other antiferment-adsorbents heretofore considered.

#### EMULSIONS OF NORMAL AND PATHOLOGIC SKIN

The author's results with injections of skin emulsions may be made to harmonize logically with the foregoing. The experimental data which strengthen the case for a non-specific mechanism in the case of agar, luetin, pallidin, placentin, have not yet been developed. Clinically there is nothing suggestive of specificity about the results, even Sellei's<sup>42</sup> conclusions in regard to "homaesthesia" being unsubstantiated by this work. In normal skins with emulsions of normal skins, reactions as distinctive apparently as the papular luetin reaction can be produced. A provisional test with boiled emulsion makes it likely that the same reaction can be duplicated with all suggestion of ferments in the injected material ruled out. In a late syphilitic, a normal-skin emulsion produced the picture of a pronounced, tho not pustular, luetin reaction. In another psoriatic, otherwise normal, the reaction was mild, even doubtful. The anti-enzyme-adsorbent power of such suspensions would either seem to be somewhat inferior to that of suspensions containing organisms (palladin, bubo extract, etc.), or else the low protease content of normal human serum affects the reaction. The nearest approach to specificity was in the case of pityriasis lichenoides chronica, which reacted both to a psoriatic-lesion emulsion and to his own lesion emulsion on two occasions and indefinitely the third time. Even this can be easily accounted for in the theory by the marked difference in composition of the normal and pathologic emulsions. The reaction was not really specific for pityriasis lichenoides chronica, but simply for an extract of a tissue showing a marked content of scales and leukocytes, for example, typical of psoriasis as well as of pityriasis lichenoides chronica. It is of course impossible to say what difference this would make in antiferment adsorptive power. It is, however, quite as reasonable to expect a difference between normal and pathologic tissue here as between various tissues in the adsorptive phenomena of the Abderhalden reaction.

<sup>42</sup> Berl. klin. Wchnschr., 1910, 47, p. 1836.

## MISCELLANEOUS CONSIDERATIONS

The writer has purposely limited his discussion to the reactions mentioned, in order not to obscure the issue with too great a mass of details, many of them of uncertain application. The production of local intradermal reactions by colloidal silver suspensions (electrargol) has been described by Hift,<sup>43</sup> and "non-protein anaphylaxis" to atoxyl and other substances has been described. Hift states that he could not secure the reaction on first injection. The status of reaction to a colloidal metal may, of course, be that of any other colloidal antiferment adsorbent, altho it may be recalled that Bordet<sup>19</sup> could secure no anaphylatoxin-formation with a colloid such as silicic acid. To those who interpret the behavior of adsorbents as disturbances of colloid equilibrium, however, such an explanation of the reported behavior of electrargol would be rational.

The cutaneous tuberculin reaction is also of some interest in this connection. Perkel<sup>44</sup> quotes Wolff-Eisner<sup>45</sup> as having attacked the specificity of the torpid form of this reaction on the ground that autopsy on patients presenting it showed no demonstrable evidence of tuberculosis. Killed tubercle bacilli have been shown to cause the development of bacterial anaphylatoxin in guinea-pig serum, apparently by their ferment-inhibitive capacity. Drying and grinding of tubercle bacilli does not influence their ability to produce anaphylatoxin (Doerr). The possibility that this same property is contributory to the production of seemingly non-specific and atypical von Pirquet tests, should not be overlooked.

The formation of anaphylatoxin by diphtheria toxin has been demonstrated by Friedberger and Mita<sup>46</sup> and its ability to inhibit antitrypsin by Jobling and Petersen.<sup>47</sup> It is impossible, of course, with the experimental material at present available to generalize sweepingly in regard to the mechanism of the Schick<sup>47</sup> test, which depends on an intradermal reaction produced by diphtheria toxin. The reaction itself, and its value as an index of diphtheria immunity, may involve antigen-amboceptor reactions in accord with the older theory. None the less it is suggestive, that the injected toxin adsorbs antiferments *in vitro*. It may conceivably, in those cases in which it is not inhibited by anti-toxin, uncover ferments that give rise to some extent to a proteolysis in which toxins are produced, the matrix of which is not the injected toxin, but the proteins of the patient.

The lighting-up of the original site of injection, following a 2nd injection after a supposed refractory or preparation period, in which the body produces antibodies to cope with the parenterally introduced protein, has been accepted as in line with the ordinarily conceived mechanism of active anaphylaxis. In his own experiments, the author has not thus far encountered any such reaction, regardless of the time interval between the two injections. Perkel,<sup>44</sup> however, working with luetin, has reported in his own case what he supposed was the lighting up of a negative site of injection after a 2nd injection 10 days after the 1st. Since torpid reactions have been known to light up at even longer intervals from the time of injection, his supposed anaphylactic reaction is open to

<sup>43</sup> Wien. klin. Wchnschr., 1913, 26, p. 1546.

<sup>44</sup> Arch. f. Dermat. u. Syph., 1915, 121, p. 7.

<sup>45</sup> Die Ophtalmo- und Kutan-Diagnose der Tuberculose, 1908.

<sup>46</sup> Ztschr. f. Immunitätsf., 1913, 17, p. 506.

<sup>47</sup> München. med. Wchnschr., 1913, 60, p. 2608.

the suspicion of being simply a tardive reaction. The prompter reaction in Perkel's case, with the 2nd injection, was observed by the author also in his 2nd injection of agar. The author's was made on the other arm, whereas Perkel made his within 3 cm. of the 1st. The areola of the 2nd reaction extended well around the site of reaction of the 1st. It seems possible that such close proximity led to a confusing picture. The effect of injecting a 2nd dose of antitrypsin adsorbent in the immediate field of activity of the 1st, is comparable in a local way to the effect of introducing an inhibitor of antiferment such as potassium iodid by way of the blood. The 2nd reaction is more severe, and the 1st, in which a balance had been reached, lights up when that balance is disturbed. It is not impossible that this same argument might apply in explanation of the severity, in the author's experiments, of reactions to agar which were made in regions which had already been the site of reactions to skin emulsions, etc.

#### SUMMARY

Recent conceptions in regard to the physical mechanism of anaphylaxis can be applied to advantage in clearing up the confusion incident to conflicting reports on the specificity of certain intradermal tests. Such reactions, including those to luetin and pallidin, that to agar observed by the author, to iodid (Sherrick), to placental substrates, and to skin emulsions, may be conceived as at least in part due to the parenteral introduction of antiferment-adsorbents, the activity of which uncovers ferments normally present in the subject. These proteases split up the proteins of the subject, with the formation of anaphylatoxins the action of which in turn produces focal necrosis and inflammation. On the possibility for a focal character of such a process, this statement by Jobling, Eggstein and Petersen<sup>13a</sup> is apropos: "Indeed it seems probable that the protease action can take place in what might be termed local areas of antiferment deficiency such as must occur at the point of contact of the serum and adsorbing substance." The course of the reaction is determined by the success or failure of the body cells in their effort to restore the anti-enzyme-protease balance at the site of injection of the adsorbent. The escape of locally formed toxins into the lymphatic or vascular circulation, in spite of the walling off by leukocytes characteristic of such reactions, might account for systemic symptoms. Whether the matrix of the locally formed anaphylatoxin is blood, lymph, or cellular elements of either blood or tissues, cannot be stated as yet. In general such reactions may be considered as non-specific, in opposition to the term specific as used in the antigen-antibody theory. They are conceivably due to the action of the patient's own enzymes on his own proteins, made possible by the inhibi-

tion of his antiferments, and not to a specific interaction between the injected substance and a specific amboceptor in the blood. The problem of why some persons react while others do not, is thus transferred, tho to a degree as yet undetermined, to an investigation of the changes which may occur in ferment balance locally in organs and tissues and in the body as a whole, within the limits of normal and pathologic processes. Experimental evidence is accumulating toward a substantial basis for such work. Future studies may well contribute a new method of approaching obscure problems in etiology and pathogenesis, especially in cutaneous diseases.